progenitors are $CD34^+$, $flk\text{-}1^+$ or $tie\text{-}2^+$. Support for this amendment can be found throughout the specification, e.g., page 11, line 18 and page 14, line 14-29, as well as the Examples.

Pursuant to 37 CFR 1.821-1.828, a sequence listing is enclosed herewith.

The specification was objected to and claims 1, 3, 5, 6, 9, 10 and 12-18 rejected under 35 U.S.C. §112, first paragraph. The Examiner takes the position that the specification does not enable any person skilled in the art to use the invention in view of the lack of predictability in the art. Specifically, the Examiner cites Applicant's 1997 paper in the journal *Science*, stating that "there is a lack of predictability that the skilled artisan can administer an effective amount of endothelial progenitor cells, as the resident population of endothelial cells is competent to respond to administered angiogenic cytokines."

Applicants respectfully disagree and submit that this rejection be withdrawn for the following reasons.

Applicants respectfully submit that the above statement taken from page 967 of Asahara, et al., *Science*, 1997, is not an admission that the use of the present invention would be difficult, but that the present invention is advantageous in that it may be able to overcome problems seen with administration of angiogenic cytokines alone. Please see page 4, lines 3-8 of the present specification. As applicants state at page 967, lines 10 of Asahara et al:

> A potentially limiting factor in strategies designed to promote neovascularization of ischemic tissues [cite omitted] is the resident population of ECs that is competent to respond to administered angiogenic cytokines [cite omitted]. This issue may be successfully addressed with autologous EC transplant.

In light of the above, Applicants respectfully request that the rejection withdrawn.

Claims 1, 3, 5, 6, 9, 10 and 12-18 stand rejected under 35 U.S.C. §112, first

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paragraph. The Examiner takes the position that while the specification was enabling for endothelial progenitor cells which are $CD34^+$, FLK-1^+, TIE-2^+, it does not recently provide enablement for any other endothelial progenitor cell.

While applicants respectfully disagree, the claims have been amended to recite that the EC progenitors are $CD34^+$, FLK-1^+ or TIE-2^+, ie., the subject matter noted by the Examiner as enabling. Accordingly, applicants respectfully submit that the rejection be withdrawn.

Claims 1, 3, 5, 6, 9, 10 and 12 stand rejected under 35 U.S.C. §112, second paragraph.

Applicants respectfully submit that the rejection has been obviated by the amendments to the claims, and should therefore be withdrawn.

Claims 1 and 3 stand rejected under 35 U.S.C. §102(a) as being anticipated by Asahara, et al. (*Circulation*, 1996).

Applicants respectfully disagree and request that this rejection be withdrawn for the following reasons.

Applicants note a Declaration by Drs. Isner and Asahara making it clear that each of the persons other than Drs. Isner and Asahara listed on the cited Asahara abstract were not co-inventors of the presently claimed invention is currently being executed by the inventors and will be filed under separate cover. In light of the Declaration, Applicants respectfully submit that the rejection under 35 U.S.C. §102(a) should be withdrawn. See, *In re Katz,* 215 USPQ 14(CCPA) 1982.

Claims 1 and 3 stand rejected under 35 U.S.C. §102(a) as being anticipated by Noishiki, et al., (*Nature Medicine*, 1996).

Applicants respectfully disagree and request that this rejection be withdrawn for the following reasons.

Applicants note that claim 1, as amended, requires administering an **isolated** endothelial progenitor cell. Noishiki, et al., is directed to use of transplanted bone marrow cells to induce capillary growth in synthetic vascular grafts. The use of isolated endothelial progenitor cells is not taught by Noishiki, et al., and thus there can be no anticipation. Accordingly, Applicants respectfully submit that the rejection should be withdrawn.

Claims 1, 3, 5, 9, 10 and 12-18 stand rejected under 35 U.S.C. §103 as unpatentable over Asahara, et al (*Circulation* 1996) or Noishiki, et al. (*Nature Medicine*, 1996) in view of Shi, et al. (*J. Vasc. Surg.* 1994), Bikfalvi, et al. (*Leukemia* 1994) and Asahara, et al. (*Circulation* 1995).

Applicants respectfully disagree and request that this rejection be withdrawn for the following reasons.

The present invention is based on the surprising discovery by Applicants that isolated endothelial progenitors cells selectively migrate to sites of active angiogenesis or blood vessel injury and thus can be used in treatment. See, page 4, lines 15-29 of the present specification. This is not taught, suggest or obvious by the cited references.

For the reasons noted above, Asahara, et al (*Circulation* 1996) has been removed as a prior art reference.

Noishike, et al., is directed to use of transplanted bone marrow cells to induce capillary growth in synthetic vascular grafts. The reference does not teach or suggest the use of isolated endothelial progenitor cells. The reference further does not teach or suggest administration of such isolated EC progenitors in the treatment of ischemic tissue or treatment of an injured blood vessel.

The secondary references do not make up for the deficiency of the primary references.

In light of the above, Applicants respectfully submit this rejection be withdrawn.

For the reasons stated above, Applicants respectfully submit that all of the rejections set forth in the August 5, 1997 Office Action have been overcome and that the case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this application is earnestly solicited.

Respectfully submitted,

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